

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 19-05-2005

Applicant's or agent's file reference
MH/LB 53936

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/SE 2005/000231

International filing date (day/month/year)
21.02.2005

Priority date (day/month/year)
20.02.2004

International Patent Classification (IPC) or both national classification and IPC
C12N 15/11, A61K 48/00, A61K 38/00, A61P 9/10

Applicant
INDEX PHARMACEUTICALS AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
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Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language, _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ in written format

☒ in computer readable form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☐ claims Nos. _____

because:

☒ the said international application, or the said claims Nos. 1-31
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

Present claims 1-8, 13-23, 27-29, 32-38, 44 relate to a compound defined by reference to a desirable characteristic or property, namely "an NF-kappaBp65 inhibitor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning

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☐ The claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: BOX III.2

of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds described in claims 9-12, 24-26, 30, 31, 40-43, 45, 46.

Further, the search has covered the general aspects of the invention to some extent, although it lacks the necessary precision in the definition of the subject matter. Consequently, the search for the general concept of "an NF-kappaBp65 inhibitor" will retrieve a pertinent document only if this concept is described in general terms in a reference. Specific solutions previously known and falling under the general concept - but failing to mention this fact - are likely not to be revealed in such a search.

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	32, 35-37, 40-46	YES
	Claims	33, 34, 38, 39	NO
Inventive step (IS)	Claims		YES
	Claims	32-46	NO
Industrial applicability (IA)	Claims	32-46	YES
	Claims		NO

2. Citations and explanations:

Reference is made to the following documents:

D1: HUANG, C Y. SOD 1 down-regulates NF-kappaB and c-Myc expression in mice after transient focal cerebral ischemia. Journal of cerebral flow and metabolism, 2001, Vol. 21, No. 2

D2: WO03041640 A2

D3: WO9747325 A1

D4: WO03070918 A2

D5: US2001002391 A1

D6: US5994402 A1

After a primary ischemic injury, which predominantly results in necrosis, there is a secondary injury in the neighbouring tissue, due at least to some extent to apoptosis. This secondary damage is usually not evident until several days after the initial ischemic event.

The invention relates to methods of preventing, treating and/or alleviating secondary ischemic damage in a mammalian organ or tissue, comprising a step of administering an effective amount of an NF-kB inhibitor to said organ or tissue. Compositions for this purpose are also disclosed.

D1 describes a method where SOD1 overexpression attenuates activation of NF-kappaB thereby reducing ischemic damage, see abstract. Animals used in the investigation were subjected to cerebral artery occlusion (MCAO) and reperfusion, see abstract. According to D1, NF-kappaBp65 is

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inhibited by SOD1, see pages 165-169, under "Results". From D1, it is known to inhibit ischemic damage in brain.

The invention according to claims 34 and 38 is therefore not considered novel in relation to D1. SOD1 is considered to be a small molecule, therefore, claim 39 is not considered novel.

Document D1 is considered to represent the closest prior art. The invention according to claim 32 differs from the method in D1 in that the ischemic damage is secondary.

Due to these features, secondary ischemic damage could be prevented or reduced.

Consequently, with the background of D1, the problem is to develop a product which prevents or reduces secondary ischemic damage.

From D1, it is known to treat ischemic damage with an NF-kappaBp65 inhibitor. It is therefore considered obvious for a person skilled in the art to treat secondary ischemic damage because the secondary ischemic damage is damage caused by an ischemic event in secondarily affected tissue. Therefore, claim 32 is not considered to involve an inventive step.

D2 relates to a method for treating or preventing ischemic reperfusion injury to an organ by administering an IKK-B inhibitor to an organ, see page 2, lines 1-20. The ischemic reperfusion injury may result from a myocardial infarct and angioplasty. The damage is treated or prevented because dnIKK-B inhibits NF-kappaBp65, see page 5, line 16-page 6, line 16.

The invention according to claim 33 is therefore not novel

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in relation to D2.

The invention according to claims 35-37 differs from the use in D2 in that the myocardial infarct is secondary. Due to these features, secondary myocardial infarction could be prevented or reduced.

Consequently, with the background of D2, the problem is to develop a method to achieve treatment or prevention of secondary ischemic damage.

It is considered obvious to a person skilled in the art that myocardial infarctions can be caused by a number of reasons. D2 describes that myocardial infarctions can be caused by, for instance, an ischemic injury or angioplasty. From D2, it is known to prevent or reduce myocardial infarction by using an NF-kappaBp65 inhibitor. It is therefore considered obvious to a person skilled in the art to use what is known from D2 to also reduce secondary myocardial infarcts. Hence, claims 35-37 are not considered to involve an inventive step.

The invention according to claims 40-43 differs from the method in D1 and D2 in that it uses different NF-kappaBp65 inhibitors.

Due to these features, it is possible that a different effect is achieved in the prevention or treatment of ischemic damage or severity of secondary myocardial infarct.

Consequently, with the background of D1 and D2, the problem is to find an alternative NF-kappaBp65 inhibitor which prevents or treats ischemic damage or severity of secondary myocardial infarct.

From D3, it is known to use SEQ ID NO 1 and SEQ ID NO 2 as NF-kappaBp65 antisense oligonucleotides, see abstract, page 12, lines 1-15.

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Using the prior art of D1 and D2 as a starting point, a person skilled in the art trying to solve the problem stated above would, with the teachings of D3, try to use the sequences described in D3 to prevent or treat ischemic damage or myocardial infarction. Therefore, the subject-matter defined in claims 40-43 does not involve an inventive step.

Likewise, claims 45 and 46 are not considered to involve an inventive step, because it is known to a person skilled in the art that SEQ ID NO 12 and SEQ ID NO 16 can be used to inhibit NFkappaBp65, see D4 page 135, SEQ ID NO 119 and 120. The invention according to claims 45 and 46 is therefore not considered to involve an inventive step.

It is considered to relate to measures obvious for a person skilled in the art to use a second agent with an NFkappaBp65 inhibitor in a composition. D5 describes that a substance can be combined with an NF-kappaBp65 inhibitor and used for treating ischemic damage, see claims 1 and 21. The substance could be anticoagulants, see claim 22. Therefore, claim 44 is not considered to involve an inventive step.

D6 describes a method for using NFkappaB inhibitors to treat, for instance, post-ischemia or post-infarction, see claims 1-28.

The cited document D6 represents the general state of the art.

Accordingly, the invention defined in claims 33, 34, 38, 39 is not novel and is not considered to involve an inventive step. The invention defined in claims 32, 35-37, 40-46 is novel, but is not considered to involve an inventive step.

The invention is industrially applicable.

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